UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

JUL 10 1997

Ms. Marian K. Stanley
Manager: Maleic Anhydride Panel
Chemical Manufacturers Association
13 00 Wilson Boulevard
Arlington, VA 22209

Dear Ms. Stanley:

EPA has reviewed the alternative testing proposal for phthalic anhydride (PA) entitled: "Testing Proposal of the Chemical Manufacturers Association, Phthalic Anhydride Producers Task Group, in Response to EPA's Proposed Rule for Phthalic Anhydride," dated November 22, 1996, and submitted by CMA on behalf of the Phthalic Anhydride Producers Task Group.

This proposal was prepared in response to EPA's invitation for proposals for pharmacokinetics (PK) studies for the hazardous air pollutants (HAPs) listed in the proposed test rule for HAPs (61 FR 33 178; June 26, 1996). As discussed in the proposed rule, the PK studies would be used to inform the Agency about route-to-route extrapolation of toxicity data from routes other than inhalation when it is scientifically defensible in order to empirically derive the inhalation risk. The PK proposals could form the basis for negotiation of enforceable consent agreements (ECAs) that would provide for testing in lieu of some or all of the tests proposed in the HAPs rule.

The following provides a background to EPA's method of evaluating the proposed PK strategies. As you recall, in the preamble to the proposed test rule, EPA indicated that, when reviewing PK 'proposals, it would use the Gerrity and Henry (1990) decision tree as an element in evaluating the proposed PK studies. The Agency also indicated that it would use mechanistic data in determining the appropriateness of route-to-route extrapolation of the existing data base as an alternative to conducting some or all of the testing required under the proposed HAPs test rule. Pharmacokinetics and mechanistic data may be used to inform the Agency about route-to-route extrapolation when EPA determines that extrapolation from existing studies may provide sufficient data to substitute for required testing under the proposed rule. Pharmacokinetics and mechanistic data may not be used alone to substitute for proposed required testing when studies by a route other than inhalation do not exist or are deemed by EPA to be inadequate. In such cases, however, pharmacokinetics and mechanistic data may be used to support a decision that required testing could be conducted using routes other than inhalation.

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EPA has concluded that this proposed strategy offers sufficient technical merit to warrant further consideration. The Agency invites the Phthalic Anhydride Producers Task Group to consider EPA's preliminary technical analysis of the proposal, a copy of which is enclosed in this letter. Please note that this analysis, including all discussions concerning data adequacy and test procedures/methods pertains only to the adequacy of the PK proposal for its intended purpose and not to the statutory basis for issuing the HAPs rule under section 4 of the Toxic Substances Control Act (TSCA).

If, after the Phthalic Anhydride Producers Task Group has had the opportunity to review this analysis, you have a continued interest in pursuing the ECA process as an activity distinct from the test rule process, please respond to me in writing by July 3 1, 1997. Depending on the Phthalic Anhydride Producers Task Group's response, EPA will determine whether or not to proceed with the ECA process. (The procedures for ECA negotiations are described at 40 CFR 790.22(b).) Under this process, EPA would then publish a notice in the Federal Register soliciting interested parties to participate in or monitor negotiations for an ECA on phthalic anhydride. The notice would also announce a date for a public meeting to negotiate the ECA. At these negotiations EPA may raise issues, based on the Agency's further review of the proposed strategy, that differ from those contained in the preliminary technical analysis. EPA notes that, as a result of unexpected complexities arising in the review of the PK proposals and contrary to the statement in the preamble to the proposed HAPs test rule, the Agency has not been able to conclude ECAs within 12 months of the date of the HAPs proposal.

The document submitted by the Phthalic Anhydride Producers Task Group went beyond PK by including an alternate testing strategy to respond to the testing identified in the proposed HAPs test rule. EPA's evaluation of this proposal identifies changes or additions that provide for testing of phthalic anhydride as an alternative to the testing contained in the proposed HAPs test rule. If this testing is incorporated into an ECA that is successfully concluded between EPA and the Phthalic Anhydride Producers Task Group, and if the data resulting from testing under the ECA are acceptable to the Agency, such testing will provide an alternative to some or all of the testing proposed for this substance in the HAPs test rule. If testing under the ECA does not fulfill the Agency's needs, EPA reserves the right to meet these needs through rulemaking.

EPA notes that the Phthalic Anhydride Producers Task Group makes certain assumptions regarding the interpretation and use of the available toxicological database for phthalic anhydride. The testing requirements for phthalic anhydride in the proposed HAPs test rule were identified by EPA for the purpose of providing a database to permit the assessment of residual risk following the implementation of the maximum achievable control technology (MACT) standards required by the Clean Air Act. EPA must apply rigorous standards to determine the adequacy of studies to be used for route-to-route extrapolation. Although, as stated earlier in this letter, EPA considers its current analysis of the phthalic anhydride studies to be preliminary, the

Agency will be prepared to discuss all issues in detail with the Phthalic Task Group Anhydride Producers if theAgency decides to proceed with the ECA process.

It is important that member companies of the Phthalic Anhydride Producers Task Group recognize the importance of responding to the request for comments on the proposed HAPs rule. The submission of a PK proposal to develop an ECA to conduct testing alternative to that contained in the HAPs test rule is no guarantee that EPA and the Phthalic Anhydride Producers Task Group will, in fact, conclude such an agreement. Therefore, I urge the companies to submit comments on the HAPs proposed rule as an activity separate from the ECA process. Please submit three copies of your written comments on the proposed HAPs test rule, identified by document control number (OPPTS-42187A; FRL-4869-1) to: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Document Control Office (7407), Rm. G-099,401 M St., SW, Washington; DC 20460.

In sum, EPA would like to thank the Phthalic Anhydride Producers Task Group for your creative and thoughtful initial proposal. If you have any technical questions about EPA's comments on your proposal, please contact Annie Jarabek at (919) 541-4847 (voice), (919) 541-18 18 (fax), or jarabek.annie@epamail.epa.gov (e-mail). For questions about the ECA process, please contact Richard Leukroth at (202) 260-0321 (voice), (202) 260-8850 (fax), or leukroth.rich@epamail.epa.gov (email).

Sincerely,

Charles M. Auer
Director
Chemical Control Division

Enclosure

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Preliminary EPA Technical Analysis of Proposed Industry **Pharmacokinetics (PK)** Strategy for Phthaiic **Anhydride (PA)**

July, 1997

Chemical Name: Phthalic Anhydride

CAS No.: 85-44-9 **Molecular Weight:** 148.11

Vapor Pressure: < 0.05 torr at 20 °C **Chemical Formula:** $C_8H_4O_3$

PK Proposal Submitted by: The Chemical Manufacturers Association's Phthalic Anhydride Producers Task Group, dated November 21, 1996, and entitled "Testing Proposal of the Chemical Manufacturers Association, Phthalic Anhydride Producers Task Group, in Response to EPA's Proposed Rule for Phthalic Anhydride".

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Preliminary EPA Technical Analysis of Proposed Industry Pharmacokinetics (PK) Strategy for Phthalic Anhydride

(1) Introduction

EPA is providing the following preliminary technical analysis and suggestions in response to a proposal by the Phthalic Anhydride Producers Task Group for conducting pharmacokinetics (PK) studies and additional toxicity testing for phthalic anhydride (PA). This proposal was prepared in response to EPA's invitation for proposals for pharmacokinetics (PK) studies for the hazardous air pollutants (HAPs) listed in the proposed test rule for HAPs (61 FR 33178; June 26, 1996). As discussed in the proposed rule, the PK. studies would be used to inform the Agency about route-to-route extrapolation of toxicity data from routes other than inhalation when it is scientifically defensible to empirically derive the inhalation risk. The PK proposals could form the basis for negotiation of enforceable consent agreements (ECAs) that would provide for testing in lieu of some or all of the tests proposed in the HAPs rule. (The procedures for ECA negotiations are described at 40 CFR 790.22(b).) Accordingly, this analysis, including all , discussions concerning data adequacy and test procedures/methods pertains only to the adequacy of the PK proposal for its intended purpose and not to the statutory basis for issuing the HAPs rule under section 4 of the Toxic Substances Control Act (TSCA).

Pharmacokinetics and mechanistic data may be used to inform the Agency about route-to-route extrapolation when EPA determines that extrapolation from existing studies may provide sufficient data to substitute for required testing under the proposed rule. Pharmacokinetics and mechanistic data alone may not be used to substitute for proposed required testing where studies by a route other than inhalation do not exist or are deemed by EPA to be inadequate. In such cases, however, pharmacokinetics and mechanistic data may be used to support a decision that required testing could be conducted using routes other than inhalation.

EPA acknowledges that if an ECA is successfully concluded between the Agency and the Phthalic Anhydride Producers Task Group that provides far PK studies and other testing and if the data resulting from testing under the ECA are acceptable to the Agency; such testing will provide an alternative to some or all of the testing proposed for this 'substance in the HAPs test rule. If testing under the ECA does not fulfill the Agency's needs, EPA reserves the right to meet these needs through rulemaking.

(2) Toxicokinetic Properties

PA is slightly soluble in water and decomposes to phthalic acid. The Threshold Limit Value-Time Weighted Average (TLV-TWA) is 1 .O ppm (6.1 mg/m^3) (ACGIH; 1992). Phthalic anhydride is a potent skin, eye, and upper respiratory tract irritant. Workers exposed to

mixtures of phthalic acid and PA have been shown to develop conjunctivitis, bloody nasal discharge, atrophy of the nasal mucosa, hoarseness, cough, occasional bloody sputum, bronchitis, emphysema, and asthma. Skin sensitization with occasion urticaria and eczematous response have also been documented. Workers exposed to flaked PA (3 - 13 mg/m^3 TWA) showed rhinitis, chronic bronchitis, and work-associated asthma with latency for respiratory symptoms in the range of 1 month to 16 years (ACGIH, 1992).

Phthalic anhydride is expected to be hydrolyzed rapidly and completely to phthalic acid once in the body. Inhaled PA deposited from the airstream reacts with the aqueous environment of respiratory tract tissue and produces an irritant effect at low inhaled concentrations. At higher concentrations, some PA may break through the respiratory tract barrier and pass into the blood stream, but this is expected to be rapidly hydrolyzed to phthalic acid. Thus, as with maleic anhydride, the respiratory tract deposition efficiency and high reactivity of PA support its designation as a Category 1 gas (U.S. EPA, 1994); but subsequent systemic distribution of phthalic acid following hydrolysis of PA raises concerns for potential remote effects.

(3) Proposed Phthalic Anhydride Panel PK Strategy

This section describes the key aspects of the industry proposed ECA PK strategy entitled: "Testing Proposal of the Chemical Manufacturers Association, Phthalic Anhydride Producers Task Group, in Response to EPA's Proposed Rule for Phthalic Anhydride (61 Fed. Reg. 33178, June 26, 1996)".

The. Phthalic Anhydride Producers Task Group proposed to generate data -on blood levels for PA and phthalic acid following both inhalation and oral administration of PA to determine if data collected from studies using the oral route of administration for PA and phthalic acid can be used to describe the potential for systemic toxicity following inhalation exposure of PA. Phase I will include experiments to characterize the *in vitro* hydrolysis rate of ^{14}C-PA to ^{14}C-phthalic acid and to determine the percentage of radiolabel in blood that binds to dissolved proteins during *in vitro* incubation. Phase.1 data will be used to aid study design of the proposed blood level studies (Phases 2 and 3). Blood radioactivity after exposure to labeled compound (^{14}C-PA) will be monitored during the start of exposures and for up to 72 hours. post-exposure in Phase 3. Exposures for inhalation will be for both a single six-hour duration and a two-week regimen of 6 hours per day, 5 days per week. Oral exposures will be either a single dose or a two-week feeding regimen. A single inhalation exposure concentration and a single oral dose level were proposed;

The Phthalic Anhydride Producers Task Group proposed to perform a single four-hour acute and a 90-day subchronic inhalation study to characterize the portal-of-entry effects. The Phthalic- Anhydride Producers Task Group proposed to perform these inhalation studies using a mixed vapor 'and dust atmosphere generated from saturated PA vapor streams which are filtered fractionally to remove nonrespirable particles, unless the mixed atmospheres can not

be generated reproducibly or if the maximum concentration of a mixed atmosphere is not appreciably different from the maximum achievable concentration (MAC) for PA. The acute study was proposed at a single exposure level, the maximum attainable vapor and dust concentration, unless effects were noted. Three exposure concentrations and a control were proposed for the **90-day** study. In addition, a respiratory sensitization study in guinea pigs was proposed.'

Neurotoxicity, developmental toxicity and neurotoxicity were not explicitly addressed in this proposal. A respiratory sensory irritation study in guinea pigs was proposed. The Phthalic Anhydride Producers Task Group did not believe that carcinogenicity testing was necessary since a series of genotoxicity tests indicated that PA was not mutagenic. The Phthalic Anhydride Producers Task Group disagreed with the EPA concern about acylation, stating that it may only be appropriate for potent acylating agents since not all acylating materials are carcinogenic. In addition, the 1979 **NTP/NCI** bioassay **(NTP/NCI,** 1979) in which rodents were fed PA suggested **NOELs** at > 750 mglkgtday for rats and > 4671 **mg/kg/day** and 3434 **mg/kg/day** in male and female mice. Finally, DNA **adduct** studies were not considered appropriate due to low level human exposures.

Table 1 compares the testing provisions described in the proposed **HAPs** test rule with the PK proposal submitted by the Chemical **Manufacturers** Association's Phthalic Anhydride Panel. This table also **summarize**s EPA's preliminary response to the Panel's PK proposal. Detailed discussion of EPA's preliminary technical analysis are presented in section 4 of this preliminary technical analysis.

TABLE **1. Summary Comparing Proposed Testing Requirements for PA**

Testing	Acute	Subchron	Neuro (A & SC)	Develop	Repro	Immun Screen	Cancer/ Genetox
Proposed HAPs Rule	X	X	X	X	X	X	X
PA Panel PK Proposal	X[a]	X[b]	_[c]	_[d]	_[e]	_[f]	_[g]
Preliminary EPA Response to PK Proposal	X[1]	X[2]	P(R)[3]	P(R)[4]	X[5]	X[6]	P(R)[7]

X Testing requirement in the proposed **HAPs** test **rule.**
P Provisional determination
R Route-to-Route

Acute toxicity testing:

X' Single concentration **4-hr** exposure with limited histopathology is proposed. BAL and macrophage **function** is not included. Alarie respiratory sensory irritation assay is not included. Respiratory **sensitization** study in guinea pigs is proposed to measure airway resistance, serum globulins to PA, PA-guinea pig serum albumin (PA-GPSA) and GPSA and histopatboiogy on high and control groups receiving induction and challenge.

X[1] EPA maintains that the proposed acute study is needed and should be performed at more than one concentration and include histopathology for the respiratory tract, liver, and kidney, the BAL and macrophage function assays as called for in EPA's upcoming health effects test guideline, ***TSCA*** Acute ***Inhalation Toxicity with Histopathology,*** which is the acute protocol to be required in the proposed **HAPs** Test Rule. EPA notes that the Alarie respiratory sensory irritation assay may be superfluous under an acceptable ECA, since additional PK and mechanistic dam would be obtained.

Subchronic toxicity testing:

X[b] **The** Phthalic Anhydride Producers Task Group proposed a 90day inhalation study to mixed vapor and dust at three exposure concentrations with a control.

X[2] EPA maintains that **the** proposed **90-day** inhalation study is needed and strongly suggests additional interim sacrifices and a recovery satellite study be performed to inform about the choice of dose metric and would allow the Agency a means to reconsider the need for **carcinogenicity** testing as described in the proposed **HAPs** Test Rule..

Neurotoxicity testing (A & SC):

-[c] The neurotoxicity testing need is not **explicitly addressed** in this proposal; blood level determinations of both PA and phthalic acid is proposed to de&mine if data collected from studies using the oral route can be used to describe potential for **systemic** toxicity.

P(R)[3] EPA maintains that there are not sufficient data on either acute or subchronic inhalation neurotoxicity **of PA** and believes this proposed **HAPs** Test Rule testing is needed. **However,** under an acceptable ECA. EPA could agree to reconsider the need for neurotoxicity testing if certain triggers are met. These triggers might provide that (1) blood levels of PA or phthalic acid are not **sufficient** to warrant **concern** after **inhalation** exposures to PA in the PK studies, **and** (2) significant **portal-of-entry effects** are associated with these PA or **phthalic** acid blood levels. EPA believes that, as an alternative. under an acceptable ECA, these **studies could be** performed via tbe oral route, if quantitative route-to-route extrapolation can be developed. See section 4 for additional details..

Developmental toxicity testing:

-[d] **The** developmental toxicity testing need was not explicitly addressed in this proposal. Blood leveldeterminations in rats were proposed to generate **data** that will facilitate use of existing **oral** studies. Developmental effects **after** oral **administration** were associated with maternal toxicity at TD_{05} **= 55 mg/kg/day (Dixon** et al., **1978;** Fabro et **al.,** 1977.1982) in mice.

P(R)' EPA believes that there are **not sufficient** data on the developmental toxicity of inhalation **exposures** to PA that address this data need and beliies **the** proposed **HAPs** Test Rule testing is needed. However, under an acceptable ECA, EPA could agree to reconsider **the** need for developmental toxicity testing if certain triggers are met. These triggers might provide that (1) blood levels of PA or phthalic acid are not sufficient to warrant concern after inhalation exposures to PA in the PK studies, and (2) significant portal-of-entry effects are associated with these PA or phthalic acid biood levels. EPA believes that. as an **alternative,** under an acceptable ECA. these studies could be performed via the oral route, if quantitative route-to-route extrapolation can be developed. See section 4 for additional details.

Reproductive toxicity testing:

-[e] **The** reproductive toxicity mating need was not explicitly **addressed in this proposal.**

X[5] EPA believes tbat there are not **sufficient** data on the reproductive toxicity of inhalation **exposures** to PA that address this data need and believes the proposed **HAPs** Test Rule testing is needed. EPA **believes** that **the research** of Dr. Paul Foster (Foster, P. **1997)** of **the** Chemical Industry Institute of Toxicology **(CIIT)** may assist in meeting this data need. As an alternative. under an acceptable ECA, EPA could agree to reconsider the need for **reproductive** toxicity

testing if certain triggers are met. These triggers might provide that (1) blood levels of PA or phthalic acid are not sufficient to warrant concern after inhalation exposures to PA in the PK studies, and (2) significant portal-of-entry effects are associated with these PA or phthalic acid blood levels. EPA believes that, as an alternative, under an acceptable ECA, these studies could be performed via the oral route, if quantitative route-to-route extrapolation can be developed. See section 4 for additional details.

Immunotoxicity testing:

-[f] The panel proposed a respiratory sensitization study in guinea pigs to measure airway resistance, serum globulins to PA, PA-guinea pig serum albumin (PA-GPSA) and GPSA with histopathology on high and control groups receiving induction and challenge. SRBC assay not included.

X[6] EPA believes that the SRBC assay is needed as described in the proposed HAPs Test Rule and agrees with the proposed sensitization study.

Carcinogenicity/Genetox testing:

-[f] No carcinogenicity testing is proposed based on the lack of mutagenicity in a series of genotoxicity tests (Florin et al.. 1980; Galloway et al., 1987; Phillips et al., 1986; Shelby and Stasiewicz, 1984; Zeiger et al., 1985). Acylation concern is discounted on the basis that it may only be appropriate for potent acykting agents since not all acylating materials are carcinogenic. The need for DNA adduct studies is discounted on the assertion that humans are exposed at low levels. Also cited is that the NOEL for oncogenicity in NTP/NCI oral bioassay > 750 mg/kg/day for rats and > 4671 mg/kg/day and 3434 mg/kg/day in male and female mice (NTP/NCI, 1979).

P[7] Under an acceptable ECA, the demonstration of the lack of mutagenicity and DNA binding, together with identification of a NOAEL for cytotoxicity of PA in the 90-day study, as well as characterization of the (C x t) considerations of effect and recovery may he sufficient to allow EPA. to reconsider the requirement for a two-year cancer bioassay. EPA believes that the proposed gas-phase testing (to maximize PA exposure) in *S. Typhimurium* as well as DNA biii assays, should include a positive control of a known acykting agent, such as dimethylcarbamoyl chloride (DMCC). If sufficient blood kvels of PA or phthalic acid to warrant concern for remote effects are demonstrated in the inhalation PK study, then EPA notes that the proposed PK work or development of a dosimetry model would provide predictions that could serve to inform the Agency about the comparison of measured and prediited blood kvels with effect levels from the existing oral cancer bioassay (NTP/NCI, 1979). See section 4 for additional details.

4) EPA Comments on PA Panel PK Strategy

EPA has reviewed the proposal for a PK strategy to address the data need for PA. This section provides detailed comments on the various components of the proposal and summarizes requirements that must be met in order for the proposal to be found acceptable.

EPA wishes to emphasize that the objective of the HAPs Test Rule is to generate data necessary to characterize dose-response for chemicals that have already demonstrated significant exposure. The considerations to be addressed by this PK strategy are those limited to evaluating the dose-response of potential toxicity, i.e., characterizing levels at which toxicity is demonstrated. Consideration of comparing the dose-response estimate to exposures is relegated to risk characterization.

EPA agrees with the industry proposal that additional work on PA should focus primarily on the respiratory tract as the principal and limiting target of PA toxicity. EPA views directed PK work as essential to substantiate that stance in the absence of data on required endpoints at remote (systemic) target sites. The proposal does not adequately establish how the obtained PK and mechanistic data might be interpreted or used to inform route-to-route extrapolation; thus, it is not clear how these data would be used to establish that the critical toxicity is limited to initial contact site in the respiratory tract after PA inhalation, with insignificant delivery of phthalic acid to remote sites after PA hydrolysis; so that toxicity tests for effects of PA on systemic target tissues are not warranted. EPA has made some suggestions to that end in its comments.

PK Model: EPA concludes that the proposed PK protocol to generate data on the blood timecourse radiolabel profiles of PA and phthalic acid appears appropriate to generate data to serve as the basis for quantitativeroute-to-route comparisons: EPA notes, however, that only one concentration was proposed for the repeated oral and inhalation exposures. EPA believes that only one concentration limits the usefulness of these data for extrapolation of the existing oral data at various levels and to evaluate the proposed 90-day study at various concentration levels. Exposure levels should match those exposure levels proposed for route-to-route comparisons. As an alternative, development of a dosimetry model to describe the disposition of PA and phthalic acid would provide the flexibility to allow. quantitative extrapolation of the dose-response relationships in the existing and proposed studies. EPA also notes that if a model to address systemic disposition of phthalic acid is to be developed, then the concentration of phthalic acid in the urine will be needed to determine total mass balance.

The Phthalic Anhydride Producers Task Group was not explicit 'as to how inhalation exposure levels would be linked back to the existing oral data base on pertinent endpoints. The basis for monitoring blood levels after each route of administration is to demonstrate that there is low potential for systemic toxicity due to conversion of PA to phthalic acid. If the phthalic

acid levels achieved via inhalation are greater than those achieved via oral dosing which are associated with adverse effects, theninhalation testing for remote effects would be needed to fully characterize the extent of effects resultant from concentrations achieved by inhalation. In order to establish the internal dose associated with the exposure levels of the existing oral toxicity data, EPA maintains that the administration vehicle and the exposure concentration must be the same as that for the oral data intended as the basis of quantitative route-to-route extrapolation. For example, since the availableNTP/NCI bioassay (NTP/NCI, 1979) administered PA in the diet, the proposed gavage, as a dietary slurry of PA (vehicle and ground rodent chow), is the closest approximation to diet administration in the NTP/NCI bioassay and would be needed, as the vehicle for extrapolation of the data from this oral study. However, the proposal did not address how PK data in rats would be used to assess the developmental data need, where toxicity data are associated with an oral dosing of 55 mg/kg/day in mice. The relationship between mice and rats will need to be established in order to address this extrapolation.

The proposal also alludes to the availability of additional data on phthalic acid, but does not cite these references. EPA agrees that PA will be hydrolyzed rapidly to phthalic acid, and would consider evaluating internaldose levels of phthalic acid achieved in these studies as the basis of quantitative route-to-route extrapolation; however, these data on phthalic acid must be provided to the Agency for evaluation. These data may be particularly useful if studies were performed in rats, since the 'proposed PK work is to be done in that species.

EPA is concerned about the capabilities to characterize the deposition and bioavailability of the proposed mixed vapor and particle exposures or the inhalation PK and toxicity studies. The Amoco Corporation (1988) showed hemorrhagic foci after exposures to 500 $\mu g/m^3$ (0.08) ppm PA, 6 hours/day, 5 days/week for 3 weeks. The MAC cited in the industry feasibility studies was 11 mg/m^3 (1.8 ppm), which appears to leave considerable "room" for vapor-only testing and eliciting a NOAEL and LOAEL. Thus, EPA believes that at least one concentration is tested as a vapor only at or near the MAC. If the mixed vapor and dust atmosphere can be generated reproducibly and is also employed, the aerosols must be inhalable by the test species and characterized by mass median aerodynamic diameter (MMAD) and geometric'standard deviation (σ_g).

*Acute and **Subchronic Toxicity** Testing:* While EPA agrees that PA is established as an irritant and sensitizer, the purpose of the HAPs Test Rule is to acquire data that allows characterization of the dose-response after inhalation exposure. Thus, more than one concentration is required to establish this relationship in the proposed acute toxicity study. EPA notes the provision for the trigger of an additional 8-hr or 1-hr study based on the results, as stipulatedin ***EPA's upcoming health** effects test* guideline, ***TSCA** Acute **Inhalation Toxicity** with **Histopathology***, which is the acute protocol to 'be required in the proposedHAPs Test Rule.. As recommended in these guidelines, the BAL and macrophage function assay is needed to adequately characterize respiratory tract effects. These assays can be readily

addressed as satellites to the proposed inhalation testing. EPA notes that the Alarie respiratory sensory irritation assay (ASTM E 981-84) *may be superfluous* under a acceptable ECA, since additional PK and mechanistic data would be obtained. The acute inhalation study should include histopathology for the respiratory tract, liver, and kidney.

EPA agrees with the proposed 90-day study. In addition to the entire respiratory tract, liver and kidney histopathology is appropriate given the known targets of phthalic-acid. EPA suggests that additional interim sacrifices would provide insight on whether concentration (C), duration_(t), or the (C x t) product is the dominant determinant of toxicity and, thereby would inform about the choice of appropriate dose metric. EPA suggests that a satellitegroup to study'recovery of lesions would enhance evaluation of the assertion that carcinogenic&y of PA in the respiratory tract is not likely and would allow the Agency a means to reconsider the need for carcinogenicity testing as described in the proposed HAPs Test Rule. If the 90-day study identifies the NOAEL for nasal irritation, and the absence of mutagenicity or DNA binding is demonstrated for PA (see below), it could be argued that potential tumors wouldhave to result from cytotoxicity and subsequent cellular proliferation as precursor events (see carcinogenicity/genotoxicity section).

Neurotoxicity *Testing:* EPA maintains that there are not sufficient data on either acute or subchronic inhalation neurotoxicity of PA to address this data need and that this proposed HAPs Test Rule testing is needed. However, under an-acceptable ECA, EPA could agree to reconsider the need for neurotoxicity testing if certain triggers are met. These triggers might provide that (1) blood levels of PA or phthalic acid are not sufficient to warrant concern after inhalation exposures to PA in the PK studies,- and (2) significant portal-of-entry effects are associated with these PA or, phthalic acid blood levels. EPA believes predictions using a PK model would also inform the Agency about these considerations. The significance of phthalic acid levels in the blood after inhalation exposure in the PK studies will be judged in comparison to the blood levels obtained with oral dosing in the PK studies and in comparison to effect levels in acute and subchronic studies (existing studies as well as ECA studies). EPA has no knowledge of neurotoxicity testing data available on PA or phthalic acid after oral exposures that could be used for comparison with PA or phthalic acid blood levels achieved after inhalation exposures. If, based on the relevant information, the triggers are not met, then EPA will maintain that the acute and subchronic inhalation neurotoxicology battery is needed as described in the proposed HAPs Test Rule. As an alternative, under an acceptable ECA, these studies could be performed via the oral route, if quantitative route-to-route extrapolation can be developed.

Developmental Toxicity Testing: EPA maintains that there are not sufficient data on the developmental toxicity of inhalation exposures to PA that address this data need and believes that the developmental toxicity testing as described in the proposed HAPs Test Rule is needed. However, under an acceptable ECA, EPA could agree to reconsider the need for developmental toxicity testing if certain triggers are met. These triggers might provide that (1) blood levels of PA or phthalic acid are not sufficient to warrant concern after inhalation

exposures to PA in the PK studies, and (2) significant portal-of-entry effects are associated with these PA or phthalic acid blood levels. If, based on the relevant information, the triggers are not met, then EPA will maintain that the developmental toxicity testing is needed as described in the proposed HAPs Test Rule. EPA notes that the Phthalic Anhydride Producers Task Group's proposal does not address how the two species testing requirement identified in the proposed HAPs test rule will be met since model development is only proposed for one species (rat).

EPA believes that the existing oral developmental toxicity data in mice may be useful to determining the significance of resultant blood levels of PA and phthalic acid in the inhalation PK study, and agreement to rely on these data would be linked to the development of quantitative route-to-route extrapolation under an acceptable ECA. It is EPA's understanding that quantitative route-to-route extrapolation would require characterization or modeling of the disposition of PA and phthalic acid after oral administration and inhalation exposure in mice. The blood levels would also have to be compared with PA or phthalic acid levels that result from inhalation exposures to PA associated with portal-of-entry. EPA believes that, as another alternative, under an acceptable ECA, these studies could be performed via the oral route, if quantitative route-to-route extrapolation can be developed.

Reproductive Toxicity Testing: EPA concludes that there are not sufficient data on the reproductive effects toxicity of inhalation exposures to PA that address this data need and believes that the reproductive toxicity testing as described in the proposed HAPs Test Rule is needed. EPA is aware of research by Dr. Paul Foster of the Chemical Industry Institute of Toxicology (CIIT) who reported no remarkable reproductive effects in oral testing of phthalic acid in the late 1970's (Foster, P. 1997). This work may assist in meeting the reproductive toxicity testing requirement. As another alternative, under an acceptable ECA, EPA could agree to reconsider the need for reproductive toxicity testing if certain triggers are met. These triggers might provide that (1) blood levels of PA or phthalic acid are not sufficient to warrant concern after inhalation exposures to PA in the PK studies, and (2) significant portal-of-entry effects are associated with these PA or phthalic acid blood levels. EPA believes that predictions using a PK model wouldalso inform the Agency about these considerations. The significance of PA or phthalic acid levels in the blood after inhalation exposure in the PK studies will be judged in comparison to the blood levels obtained with oral dosing in the PK studies and in comparison to effect levels in acute and subchronic studies (existing studies as well as ECA studies). If, based on the relevant information, the triggers are not met, then EPA will maintain that the reproductive toxicity testing is needed as described in the proposed HAPs Test Rule. If after these considerations, a concern for reproductive toxicity remains,. then EPA believes that under an acceptable ECA, these studies could be performed via the oral route, if quantitative route-to-route extrapolation can be developed.

***Immunotoxicity** Screen:* EPA agrees that the proposed guinea pig study is appropriate to characterize the potential for PA sensitization. However, due to PA's demonstrated immunotoxic activity, EPA maintains that the SRBC assay is needed as described in the

proposed HAP's Test Rule in order to characterize potential effects on other aspects of immune function. EPA believes that circulating cytokines or antibodies secondary to the demonstrated portal-of-entry effects could have systemic effects. This assay can be addressed as a satellite to the proposed inhalation testing,

Carcinogenicity/Genetox *Testing:* EPA is concerned about the possibility that PA may be carcinogenic via the inhalation route. Both dimethylcarbamoyl chloride (DMCC) and diethyl carbamoyl chloride (DECC), two direct-acting acylating rodent carcinogens, have been demonstrated to form DNA adducts in vitro at pH 7.0-7.5 and 37 C (Segal et al. 1982). Both bis(chloromethyl)ether (a direct-acting alkylating agent) and DMCC are hydrolyzed rapidly under aqueous conditions, yet both are potent inhalation carcinogens. PA is not expected to be as potent a carcinogen as DMCC, but it does have the potential to bind to DNA under physiological conditions so that thepotential cancer hazard by the inhalation route must be characterized.

EPA believes that the existing mutagenicity studies for PA were actually investigations of the mutagenicity of phthalic acid due to theexperimental conditions and the ready hydrolysis of PA. As such, they do not address concern for the potential of PA to induce carcinogenicity in the respiratory tract. To address this experimental constraint of the existing genotoxicity data, EPA believes gas-phase exposure testing (Pegram et al., 1996) in *S. Typhimurium is* needed. However, because the efficacy of this system for testing acylating agents is unknown, EPA believes that the use of a positive control with a known acylating agent, such as dimethylcarbamoyl chloride (DMCC) should be incorporated into this test protocol. In addition, DNA binding assays, again with DMCC as a positive control, should be performed to rule out the concern for acylation..

Under an acceptable ECA, the demonstration of the lack of mutagenicity and DNA binding, together with 'the identification of a NOAEL for cytotoxicity of PA in the 90-day study, as well as characterization of the (C x t) considerations of effect and recovery may be sufficient to allow EPA to reconsider the proposed HAPs Test Rule test requirement for a two-year cancer bioassay.

If sufficient blood levels of PA or phthalic acid to warrant concern for remote effects are demonstrated in the inhalation PK study, then EPA notes that the proposed PK work or' development of a dosimetry model would 'provide predictions that could serve to inform the Agency about the comparison of measured and predicted blood levels with effect levels from the existing oral cancer bioassay (NTP/NCI, 1979).

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(6) PK Proposal Review Staff

The foliowing table lists individuals who contributed in the preparation of EPA's preliminary technical analysis of the Chemical Manufacturers Association's Phthalic Anhydride Producers Task Group PK proposal for phthalic anhydride.

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